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Devices Used as a Radiation Source (in Combination With Psoralen Drug) in the Photochemotherapy for Psoriasis

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

21 CFR Subchapter J

[Docket No. 79N-0013]

Devices Used as a Radiation Source (in Combination With a Psoralen Drug) in the Photochemotherapy for Psoriasis; Intent To Propose Rules and Develop Recommendations

AGENCY: Food and Drug Administration.

ACTION: Notice of Intent.

SUMMARY: The agency is considering safety performance recommendations for devices used as a radiation source in combination with a psoralen drug in treating psoriasis (PUVA therapy). This notice discusses concepts for improved safety of these devices. Some performance features are related to temperature control, lamp shielding, goggles, and measurement of the radiation level (dosimetry). They are based largely on the radiation safety experience gained from clinical trials in which PUVA therapy has been shown to be effective. The agency intends to examine the concepts described, as well as the comments received, and to propose at a future date safety performance recommendations for the devices. The agency requests further information on this subject and will reexamine its recommendations when significant new information becomes available. Specifically, the agency requests comments on the conceptual recommendations listed in this notice and on general issues related to the safe use of PUVA therapy devices. If it appears that the voluntary approach implemented through safety performance recommendations is not effective as a means of improving the safety of these devices, the agency will consider establishing a mandatory performance standard for PUVA therapy devices.

DATES: Comments by April 8, 1980. Data concerning the safety and effectiveness of PUVA therapy equipment may be submitted at any time.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Glenn E. Conklin, Bureau of Radiological Health (HFX-460), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3426.

SUPPLEMENTARY INFORMATION: The Food and Drug Administration (FDA), through the Bureau of Radiological Health and under the authority of the Radiation Control for Health and Safety Act of 1968 (Pub. L. 90-602, 42 U.S.C. 263b et seq.), administers an electronic product radiation control program. This authority provides for the protection of the public health and safety through development and administration of radiation safety performance standards and development of recommendations for controlling electronic product radiation. FDA also has authority under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301-392) regarding safety and effectiveness of drugs and medical devices.

Background

Psoriasis is a disfiguring and often incapacitating skin disease that affects 1 to 3 percent of the world's population. Derivatives of the photosensitizing drug psoralen are now being used along with an ultraviolet-A (UVA) radiation source to treat psoriasis in a therapy known as PUVA (psoralen + UVA). The ingestion of the drug markedly increases the patient's sensitivity to ultraviolet radiation. This effect occurs gradually, reaching a peak 2 to 3 hours after ingesting the drug. The afflicted areas are then exposed to high-intensity UVA radiation, usually from a specifically designed system, although sunlight has been used. Many of the available devices consist of banks of fluorescent lamps mounted inside a cabinet. Usually, the patient stands inside the cabinet for the duration of the treatment. The following discussion focuses on this equipment.

The ultraviolet radiation is nominally limited to the UVA region of the electromagnetic spectrum between 320 and 380 nanometers (nm). Because the shorter wavelength radiation emission is not completely eliminated from the fluoescent lamps, there is patient exposure to radiation of wavelengths shorter than 320 nm and longer than 280 nm, a wavelength range usually called the erythemal or ultraviolet-B (UVB) region of the spectrum. There is also intense visible light at wavelengths greater than 380 nm.

Each wavelength region presents a slightly different potential risk to the patient. As with erythemal radiation from the sun, overexposure to UVB radiation from a PUVA therapy unit could cause eye injury and skin burns (erythema), while repeated overexposure would be associated with skin aging and an increased risk of skin cancer. Laboratory animals treated topically with psoralen derivatives and exposed to UVA radiation developed skin tumors (Ref. 1). Exposure to UVB enhances this effect (Ref. 1). Research has shown that cells grown in tissue culture can be mutated by UVB alone or by the combination of psoralen and UVA. Therefore, the combination of psoralen derivatives and UVA should be considered as a likely carcinogen. It is also possible that psoralen derivatives concentrated in the lens of the eye may, on exposure to UVA radiation, react with lens tissue to form cataracts. The formation of cataracts could also occur after treatment if a patient is exposed to other sources of UVA radiation, such as the sun and most common fluorescent lamps. These sources of UVA radiation could activate psoralen in the lens and cause the formation of cataracts. Chronic exposure to solar UVA alone also has been implicated in cataract induction (Ref. 11).

The use of UVA radiation and orally administered psoralen has been effective in clearing a high percentage of psoriatics, many of whom did not respond to other means of treatment. Also, patients have generally remained free of lesions when given a maintenance therapy consisting of periodic treatment. Numerous patients in various clinical trials have participated; so confidence exists that PUVA therapy can be effective (Ref. 8, 9 and 10). The use of psoralen derivatives and UVA radiation in treating psoriasis represents a medical benefit. However, due to the concerns regarding long term risks of the use of potentially damaging radiation, the situation is as yet unclear whether the benefits of PUVA therapy outweigh the risks (Ref. 7).

No psoralen derivatives have been approved by FDA for treatment of psoriasis. The current use of the drug for treatment of this condition, therefore, is under notices of claimed exemption for investigational new drugs under Part 312 of the regulations (21 CFR Part 312).

Efforts by the Agency and Consultation With Advisory Groups

FDA has reviewed information about PUVA therapy from many sources, including scientific articles, manufacturers' reports, proceedings of agency scientific advisory committees, reports from professional organizations, opinions expressed by interested scientists and physicians, and results of visits to manufacturers of PUVA therapy devices.

FDA visits to six manufacturers of UVA phototherapy devices provided data on the varying extent to which

safety features, including those relating to radiation, were considered. For example, one unit provided no lamp shielding. Another unit provided no method for determining radiation dosage. Two units provided no protective eyewear. FDA also discovered that because the lamps' output generally decreases with age, the therapy device needs to be calibrated regularly.

The temperature inside the cabinet version of the device can exceed 120° F (49° C) if no cooling is provided. Even with cooling, the temperature can exceed 100° F (38° C). Protective eyewear must be worn to prevent injury, yet vision is essential for balance and orientation. The lamps must be shielded to prevent breakage and subsequent patient injury in the event of patient collapse. Other mechanical as well as electrical hazards are also a concern.

The Psoriasis and Photobiology Task Forces of the American Academy of Dermatology published in the Academy's journal a joint statement urging caution in the use of PUVA therapy until investigative evaluation could be completed (Ref. 2). The Academy refrained from recommending this treatment until questions about treatment protocols and safety have been answered. Recently, these task forces drafted provisional guidelines for PUVA therapy describing methodology that may be used by physicians with special competence in the diagnosis and treatment of psoriasis and special training and competence in photochemotherapy for treating psoriasis. The draft recommends that PUVA therapy be administered only under the constrant supervision of such physicians (Ref. 3).

The Photobiology Committee of the Illuminating Engineering Society, with the endorsement of the Society's Board of directors, has developed a statement of the risks associated with the use of UVA irradiators being used in treating psoriasis (Ref. 4). This statement has been carefully considered, and elements have been incorporated into this notice.

PUVA therapy devices have been discussed at meetings of four FDA advisory committees. The minutes and transcripts of these meetings are on file with FDA's Hearing Clerk. The General and Plastic Surgery Device Classification Panel of the Bureau of Medical Devices has recommended that the device be classified into class III, which would require premarket approval when implemented. On July 21, 1977 and March 24, 1978, the Panel also suggested that immediate action to eliminate many of the hazards of these devices is needed. The Anti-infective and Topical Drugs Advisory Committee of the Bureau of Drugs has confirmed the effectiveness of this therapy, but due to concern regarding long-term risks and the lack of data for review regarding long-term use as expressed in meetings in 1977, 1978, and 1979, the Committee is reluctant to confirm its safety. That Committee has stated that extensive information on device performance and long-term risks should be included in the package insert if the drug is approved. The agency has reviewed with the Committee the features on devices proven in clinical use to be effective. They were discussed initially within the Dermatological Subcommittee of the Anti-Infective and Topical Drugs Advisory Committee and were presented to the full Committee at several meetings in 1978. Drug manufacturers, PUVA therapy device manufacturers, and clinicians all participated in the public discussion to develop the list of needed features. The General and Plastic Surgery Device Classification Panel of the Bureau of Medical Devices recommended additional features for patient safety during its meeting on March 24, 1978. The bureau of Radiological Health's Medical Radiation Advisory Committee, during its meeting of May 9, 1978, supported the need for equipment recommendations to improve the benefits and reduce the risks of therapy. The Technical Electronic Product Radiation Safety Standards Committee, an FDA advisory group established by statute, also endorsed the development of recommendations for equipment safety features, at its meeting of June 1, 1978.

FDA appreciates and encourages the constructive efforts of the industry, professional organizations, advisory committees, and others toward development of standards for safe and effective PUVA therapy devices.

FDA is conducting biological research, evaluating devices, and supporting research on PUVA therapy. No single study is expected to provide all the necessary information. A program of research will be necessary to determine the risk of human health posed by the PUVA therapy. In addition to biological research, the agency will continue to develop methods to measure and evaluate ultraviolet emissions. The Bureau of Radiological Health also encourages users to notify that Bureau (and also the manufacturers of UVA equipment involved) of accidental radiation overexposures. Adverse reactions associated with use of the drug must, of course, be reported to the sponsor and by the sponsor to the agency, as provided in 21 CFR Part 312, while manufacturers of UVA equipment must report accidental radiation occurrences to the Bureau of Radiological Health as provided in 21 CFR 1002.30.

Conceptual Recommendations on the Use and Performance of PUVA Therapy Devices

The following conceptual recommendations are provided for consideration and comment. A brief discussion of the rationale follows the presentation of each concept. These items are expected to form the basis for future proposed recommended standards.

1. *PUVA therapy application.* The Provisional Guidelines on Oral PUVA Therapy (Ref. 3) should be the basis for physician application of PUVA therapy. Manufacturers should include these guidelines in a caution statement for physicians. This statement should accompany the device and should also state that PUVA therapy is considered investigational as a therapy for psoriasis and that the use of psoralen derivatives for this therapy has not been approved by FDA.

2. *Lamp spectral distribution.* The optical radiation emissions from lamps used in these devices should have a spectral distribution as specified in Table I below.

Table I

Wavelength band (nanometers)	Output
<310	<1
>310 to 320	1 to 3
>320 to 330	4 to 8
>330 to 340	11 to 17
>340 to 350	18 to 25
>350 to 360	19 to 28
>360 to 370	15 to 23
>370 to 380	8 to 12
>380 to 390	3 to 7
>390 to 400	1 to 3

[1] As a percent of total irradiance between 320 and 400 nanometers.

Clinical results showing efficacy and short-term safety were obtained using a source having its peak emission at 355 nm and the remainder of the distribution as shown in Table I (Ref. 4).

3. *Exposure uniformity.* The level of UVA radiation within the exposure cavity of the cabinet at any point along the vertical center axis should not be less than 30 percent of the maximum value and, similarly, at any point in any specific horizontal plane should not be less than 20 percent of the maximum value.

Uniformity of exposure of UVA radiation over the body surface is an important aspect of the dosage problem. In some therapy units on the market, the

exposure level can vary by more than a factor of two depending on placement of the body in a unit. Exposures of the head and feet areas often are difficult to control because there is less emission at the ends of the fluorescent lamps and the lamps are frequently vertical. By appropriate design of the units, this vertical nonuniformity can be reduced to 30 percent. The horizontal uniformity in UVA level is a function of the number of lamps, the reflectors, reflecting surfaces, and general geometry. It is feasible to design a standup unit in which the patient will receive approximately the same exposure on all sides. This uniformity of better than 20 percent contrasts sharply with the possible alternative approach of using a single or a few high-intensity lamps.

4. *Dosimetry.* PUVA therapy equipment should incorporate a means for the measurement of the level of UVA radiation, in terms of irradiance (W/cm^2) or radiant exposure (J/cm^2), as defined in 21 CFR 1040.10(b). The error in radiometric measurement should be no more than 20 percent from all sources when calibrated and used in accordance with the procedures and schedules supplied by the manufacturer.

Treatment of psoriatic patients requires prescription of a drug and a radiation dosage. Careful attention has been given in the clinical trials to the measurement of radiation dose, which depends on the number of lamps, the age of each lamp, and the duration of exposure.

The usual practice for therapeutic exposures of radiation is to give an exposure at a level just below that required to produce erythema. This level varies with skin type, previous solar exposure history, and previous treatment history. Depending on the practitioner, the initial exposure may be a judgment based on experience or may be based on trial exposures to small areas. However, owing to the nature of the device, the exposure the physician thinks is being given and the actual exposures delivered to the patient may be considerably different unless adequate care is taken. To err on the low side means the patient has endured a treatment with little benefit, and the total number of treatments and total energy to clear psoriatic conditions may increase. To err on the high side can lead to acute, sunburn-type burns.

Individual physicians should not be required to develop an individual dosimetry and calibration protocol. This should be provided by the manufacturer. The measurements should be representative of the exposure on the patient's body when in place in the PUVA therapy device. The manufacturer should also supply a protocol for avoiding common errors.

The radiometer incorporated in a PUVA device should be designed to avoid or minimize common sources of measurement error. (a) Most detectors respond differently to equal amounts of radiation at different wavelengths. The specific spectral response of the detector and the spectral power distribution of the lamps should be taken into account in the design and calibration of the radiometer. (b) The response of most detectors depends on the angle of the incidence of the radiation on the detector surface and should be taken into account in the design and calibration of the system. (c) The response of the detector is usually dependent on temperature. If the detector is calibrated at one ambient temperature and is used to make measurements at another temperature the calibration may not hold. Because the ambient temperature inside the PUVA unit can be much higher than ordinary room temperature, the procedures should be designed to minimize errors due to the temperature dependence of the detector.

The instructions provided to the user of the PUVA device should specify a schedule for performing the measurements. The instructions should also contain a description of the relationship between lamp output, prescribed radiation exposure, and exposure time.

5. *Timer.* PUVA therapy equipment should incorporate a timer to control the exposure time and to initiate and terminate exposure.

6. *Protection of the eyes.* Protective eyewear (goggles) should be provided with the equipment that will, if worn during treatment, protect the eyes from exposure to ultraviolet radiation. The goggles should, however, transmit enough visible light to allow the patient to see. Visual perception is important for the patient to maintain balance and for general well-being. Instructions should be provided that describe the use of protective eyewear and warn that closing the eyes alone is not sufficient protection. Instructions provided with the equipment should also describe the increased sensitivity to UVA of the eyes and other exposed tissue after the patient ingests psoralen derivatives and should alert the patient to the potential need for protective clothing or eyewear and avoiding ultraviolet radiation from other sources.

Protective eyewear is important because there is a known cataractogenic potential for ultraviolet radiation alone and for UVA radiation when used with psoralen.

7. *Temperature control.* A means should be provided to limit the air temperature within the exposure cavity to 100° F (38° C) or less. Also, there should be warnings in the product literature to physicians to ensure that they monitor patients' reactions.

Cabinet versions of PUVA therapy devices may contain as many as 72 six-foot fluorescent lamps. Manufacturers' statements indicate that, with no force ventilation to cool the unit, the temperature can exceed 120° F (49° C). The action of the drug plus radiation, the intensity of the output of the lamps, and patient reaction are all uncertain at such elevated temperatures. A recent study of cardiac stress in patients treated for psoriasis in UVA irradiators led to the conclusion that the elevated temperature during a prolonged period of standing relatively immobile could overtax the heart (Ref. 5). Again, as noted by equipment manufacturers, adequate ventilation can reduce the temperature to at least 100° F. The use of forced ventilation to reduce the cabinet temperature will be ineffective unless there is an adequate supply of cooler room air.

8. *Electrical hazards control.* The PUVA therapy devices should have all electrically conductive parts properly grounded or protected from contact under conditions of temperature and humidity encountered during the therapy so that contact with an exposed conductive surface does not place a person at risk (Ref. 6). The devices should include a means for ground fault and circuit overload protection.

For full body treatment, a patient is typically standing while wearing little or no clothing. Elevated temperatures cause perspiration that enhances the possibility of low resistance pathways for current leaks. Even without perspiration, the skin can be exposed to the unit surface, which in turn houses lamps and ballasts that carry large amounts of current. Without proper circuit design and insulation barriers, the potential for electrocution is substantial. If fluids were spilled inside the device, the hazard could be increased. In addition to hazards to the patient, there are potential hazards to the operator and to service personnel. Changing lamps, turning on the device, etc. can be a hazard if the therapy device is grounded improperly and if ground fault protectors are not included in the design. There is also the possibility of a fire breaking out due to circuit overloads, wire shorting, or use of flammable material.

9. *Protection from lamps.* The patient should not be able to come into contact with bare lamps and, in the event of

lamp breakage, should not be exposed to the broken glass.

10. *Passage, support, and observation.* The exit from the exposure cavity should open outward, be easily workable from either the inside or the outside, and be safety interlocked to terminate emission of radiation and to stop the timer. Supports that can be grasped by the patient's hands should be provided, and the floor of the exposure cavity should provide traction for bare feet whether wet or dry. Further, the PUVA therapy device should be of sufficient mechanical strength and rigidity to resist abuse, and to withstand the force of a falling person without causing electrical fire or other hazard due to collapse. An alarm device (panic button) should be provided so the patient can signal an emergency, and there should be an observation window of ultraviolet absorbing material for monitoring the patient's reaction to the treatment.

Although not directly related to radiation safety, the features discussed in the previous paragraph are important because the environment created by the radiation during therapy exposes the patient to certain risks of injury, particularly where a mishap occurs during treatment. For example, even with the restriction on minimum temperature, the interior of the therapy unit can become very hot. The combination of extreme heat and the long periods of standing that may be required as maintenance therapy progresses could cause a patient to faint. In case of an emergency, a patient should be able to open the therapy unit and exit quickly. To further protect against such emergencies, the door to the therapy unit should open and the lamps should turn off automatically, whenever a patient faints and falls against the door. This safety feature should not only protect against an accidental overexposure, but should also stop the timer so that if the treatment is restarted the exposure time remaining for a full treatment will be known exactly.

Persons or organizations wishing further information on the development of the action program for PUVA therapy devices and their use may phone or write to the contact person whose address appears earlier in this notice.

The following references are on file at the office of the Hearing Clerk, Food and Drug Administration, and may be seen in that office between 9 a.m. and 4 p.m., Monday through Friday.

References

1. Grube, D. D., R. D. Ley, and R. J. M. Fry, "Photosensitizing Effects of 8-Methoxypsoralen on the Skin of Hairless Mice—II. Strain and Spectral Differences for Tumorigenesis," *Photochemistry and Photobiology*, 25, 269–276, 1977.

2. Psoriasis and Photobiology Task Forces, American Academy of Dermatology "PUVA Statement," *Archives of Dermatology*, 113, 1195, September 1977.

3. Epstein, J. and I. Farber, Psoriasis and Photobiology Task Forces, American Academy of Dermatology, "Provisional Guidelines on Oral PUVA Therapy," 1979, *Journal of the American Academy of Dermatology* 1(2):106–117, August 1979.

4. Photobiology Committee of the Illuminating Engineering Society, "Risks Associated with the use of UV–A Irradiators Being Used in Treating Psoriasis and Other Conditions," *Lighting Design and Application*, March 1979, pp. 56–60 and *Photochemistry and Photobiology*, 30, 199–202, 1979.

5. Rhodes, A., R. Ciagone, and M. Audley, "Cardiovascular Response to PUVA Therapy," *Clinical Research*, 25, 286a, April 1977.

6. American National Standards, Inc., ANS Safe Current Limits for Electrochemical Apparatus, ANSI/AAMI, SCL 12/78, January 19, 1978.

7. R. S. Stern, et al., "Risk of Cutaneous Carcinoma In Patients Treated With Oral Methozsalen Photochemistry for Psoriases" *New England Journal of Medicine*, Vol. 300: 809 (April, 1979).

8. Parrish, J. A., T. B. Fitzpatrick, L. Tannenbaum, and M. A. Pathak, "Photochemotherapy of Psoriasis With Oral Methoxsalen and Longwave Ultra-Violet Light, *"New England Journal of Medicine*, Vol. 29:1207, 1974.

9. Wolff, K., T. B. Fitzpatrick, J. A. Parrish, et al., "Photochemotherapy for Psoriasis With Orally Administered Methoxsalen" *Archives of Dermatology*, Vol. 112: 943, 1976.

10. Melski, J., L. Tannenbaum, J. A. Parrish, T. G., Fitzpatrick, H. L. Bleich, et al., "Oral Methoxsalen Photochemotherapy for the Treatment of Psoriasis; A Cooperative Clinical Frial" *Journal of Investigative Dematology*, Vol. 68:328, 1977.

11. Zigman, S., "Near UV Light and Cataracts," *Photochemistry and Photobiology*, 26, 437, 1977.

This notice of intent is issued under the Public Health Service Act, as amended by the Radiation Control for Health and Safety Act of 1968 (secs. 356 and 358, 82 Stat. 1174–1179 (42 U.S.C. 263d and 263f)); the Federal Food Drug, and Cosmetic Act, as amended (21 U.S.C. 301–392); and authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1).

Interested persons are invited to participate in the development of an action program by submitting written comments, views, and data on the subject. Communications (preferably 4 copies) should reference the docket number appearing in the heading of this document and should be sent to the Hearing Clerk (HFA–305), Food and Drug Administration, on or before April 8, 1980. Timely comments will be considered in formulating the action program. Comments received after that date may be considered, depending on the stage of development of any standards or recommendations.

Dated: January 30, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

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